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Prognostic value of pre-treatment inflammatory markers in patients with locally advanced breast cancer (LABC) from Saudi Arabia

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ABSTRACT

Background: Inflammation is a recognized factor in cancer progression and resistance to treatments. Several studies correlated inflammatory-related peripheral blood indices to disease progression and poor survival in various cancer types and different populations. Nonetheless, inflammation is affected by the distinctive characteristics and environmental exposure of each people. *Methods:* We retrospectively analyzed the data of female patients with LABC undergoing neoadjuvant chemotherapy (NACT). Demographics, BMI, clinicopathologic characteristics, stage of the tumor, follow-up status, and response to treatment were collected. Outcomes were evaluated concerning the high and low groups of inflammatory markers based on the cut-off values of NLR and RDW. *Results:* A total of 172 patients met the eligibility criteria among patients diagnosed with breast cancer (BC) from January 2014 to December 2020. At the time of diagnosis, the mean age was (53.4± 11), BMI was (31.2 ± 6). Left BC accounted (54.7%) and the majority were moderately differentiated (51.2%), and ductal carcinoma (85.5%), ER-positive tumor in (79.1%), HER2-positive in (32%), TNBC in (9.8%). Only normal RDW and Low NLR were significantly associated with a type of response post NACT with P values (0.003) and (0.014) respectively, with significant response type complete remission (71.5%) based on the radiological evaluation**.** *Conclusion:* RDW and NLR could be applicable biomarkers to predict response after systemic therapy among LABC. The great advantage of these biomarkers depends on routine tests before treatment, and it is cost-effective in the diagnostic plan.

Keywords: inflammatory markers, Locally Advanced Breast cancer, Breast cancer prognosis.

1. INTRODUCTION

Breast cancer has been one of the types of cancers that most common effected in females and the second most common cancer overall. In 2018 over 2 million



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cases were diagnosed with breast cancer. In 2020, a number of 3954 (29%) cases were diagnosed with breast cancer among females of all ages in Saudi Arabia (Wcrf.org, 2018; GCO.iarfc, 2020). Breast cancer is a common malignancy among females in Saudi Arabia, with a prevalence of 21.8%-29% (GCO.iarfc, 2020; Alotaibi et al., 2018). A study by Al Qahtani reports that breast cancer was considered the second most prevalent malignancy (Al Qahtani, 2007). A study of a recent survey of cancer-related mortality finds that breast cancer in Saudi women is the ninth leading cause of death (Bazarbashi et al., 2007; Mokdad et al., 2014; Lozano et al., 2012).

In Saudi Arabia breast cancer curve may increase in the nearest new generation, related to population growth and age (Ibrahim et al., 2008). According to the scurvy medical record in a Research center at King Faisal Specialist Hospital, approximately 930 new patients in medical record of breast cancer were diagnosed in the year 2002 in Saudi Arabia. In 2010 a number of 5,378 patients were diagnosed with cancer in Saudi Arabia. Out of them, 1,473 (27.4%) were diagnosed as breast cancer, which considers one of the types of cancers thataffected most of the females at Saudi Arabia (Alotaibi et al., 2018). The development process of cancer has a genetic basis. Recent studies demonstrated that inflammatory response could help in this process, including progression and metastasis of malignancies (Hanahan et al., 2011; Mantovani et al., 2007; Balkwill et al., 2001). Using simple predictors may help improve outcomes, especially if it's cost-effective and routinely done before each step-in diagnosis management and follow-up.

Previous studies have demonstrated a relationship between simple inflammatory markers that reflect the inflammatory response (e.g., peripheral blood neutrophil, lymphocyte, monocytes, and platelet counts) and several types of malignancy. Both elevated neutrophils and platelets in the blood reflected a low survival in cancer patients (Schmidt et al., 2007; Riesco et al., 1970; Bambace et al., 2011). On the other hand, high lymphocytic infiltration was associated with a good prognosis, while low lymphocyte count was associated with increased mortality risk (Papaioannou et al., 2019; Bishara et al., 2008). Furthermore, raised several monocytes were associated with poor outcomes and progression-free survival (Botta et al., 2013; Lee et al., 2012). The Neutrophil-lymphocyte ratio (NLR), lymphocyte-monocyte ratio (LMR), platelet- lymphocyte ratio (PLR), which is known as inflammation-based indexes, could be used as indexes of the host immune condition and may reflect a prognostic significance in patients with different types of cancer (Yang et al., 2019).

A systematic review and meta-analysis showed that NLR has a prognostic role and is associated with overall survival (OS) and disease-free survival (DFS) in breast cancer patients (Ethier et al., 2017). Similarly, a retrospective study demonstrated that elevated PLR related with low prognosis in breast cancer patients (Krenn-Pilko et al., 2014). Moreover, NLR and PLR affect mortality risk in patients with breast cancer (Koh et al., 2015). Additionally, low LMR has a poor disease-free survival rate (DFS) in breast cancer patients with triple-negative (Goto et al., 2018). The Mean platelets volume (MPV) reflects the platelet's mean size in the blood, which could act as a marker of platelet activation, and the Platelet activation has a role in cancer progression and metastasis (Chang et al., 2019; Franco et al., 2015). Meta-analyses showed an association between the worse long-term outcomes and high NLR after treatment in various cancers, and this study was done by azab et al as a cohort of 437 women with BC showed an increase in mortality among patients with high pre-treatment NLR, which is considered a significant risk factor for mortality regardless of the chemotherapy regimen (Azab et al., 2012).

A study found that a lower LMR (<6.1) before neoadjuvant chemotherapy was an independent for the efficacy of NACT as a predictive factor (Peng et al., 2020). Up to the best of our knowledge, there is little written about the prediction of locally advanced breast (LAC) cancer outcomes by using various inflammatory markers. Our study aims to understand the impact of peripheral inflammatory response biomarkers on the response status after Neoadjuvant chemotherapy (NACT) among patients with LAC.

2. MATERIALS & METHODS

A total of 172 Patients have been confirmed as breast cancer cases by the histopathology lab result were included in this cohort retrospective study. All patients were treated between January 2014 and December 2020 at Hospital of King Abdulaziz University, Jeddah, Saudi Arabia. Patients' medical records were reviewed, and medical history, age, height, weight, calculated BMI, pathological results, and laboratory data, post-therapy radiological evaluation was collected.

The ethical committee approved the study atKing Abdulaziz University Hospital by the Biomedical Ethics Unit (#643-19). All clinical data retrieved were anonymized and compiled, ensuring patients' confidentiality. Patients with metastatic breast cancer, lacking pathological or laboratory data, lost to follow-up, those with a history of systemic inflammatory or chronic diseases such as systemic lupus erythematosus hematological disease or bone marrow disease before the treatment were excluded.

Pathological and radiological data were reviewed to determine tumor site, size, histological grade, lymph node status, metastasis (lung, brain, and bone), hormone receptor status, human epidermal growth factor receptor 2 (HER2) statuses. Estrogen and progesterone receptor stature were evaluated using immunohistochemistry (IHC). Response status was sub-grouped into four

categories based on post-therapy radiological evaluation by mammogram and breast MRI +/- CT chest abdomen and pelvic as complete remission (CR), partial remission (PR), stable disease (SD), and progressive disease (PD), patient follow-ups were reviewed and last follow up status were obtained based on radiological evaluation and consultant notes. We have collected baseline counts of neutrophil-lymphocyte and monocytes and platelets for peripheral blood parameters to calculate our inflammatory indices (NLR, LMR, and PLR). Cut-off points for NLR, LMR, and PLR were obtained from a similar study that documented the optimal ratio of 3%, 6.2%, 135%, respectively (Ma et al., 2021). For RDW, we have used a range from a focused study on breast cancer (11-14.1) (Seretis et al., 2013).

The data were entered into a secure excel sheet version 2106 and were analyzed in Statistical Package for Social Science version 21 (SPSS 21). Descriptive analysis and chi-square test were performed to assess association inflammatory parameters and response status. A P-value of <0.05 was considered significant

3. RESULTS

Clinical and pathological characteristics

After applying inclusion and exclusion criteria, a total of 172 locally advanced breast cancer patients were included in the analysis. The average female age was 53.4± 11 and an average BMI of 31.2 ± 6. Post-treatment progression and metastasis occurred in 6 patients (3.5%). Based on the status of ER, PR, HER2, 147 (85.5%) were diagnosed with ductal carcinoma, 136 (79.1%) as ER-positive, left-sided in 94 (54.7%) with histological grade 2 in 88 (51.2%) (Table 1). Response type was identified after treatment based on the radiological evaluation. The majority were with complete remission 123 (71.5%), follow-up status documented based on annual assessment and latest status of most of them were alive with complete remission 106 (61.6%) (Table 2, Figure 1 and 2).

Table 1 Clinical and pathological characteristics		n	%
Pathological type	Ductal	147	85.5
	Lobular	21	12.2
	Mixed	4	2.3
Histological Grade	G1	29	16.9
	G2	88	51.2
	G3	53	30.8
	Unknown	2	1.2
Tumor Origin	Right breast	77	44.8
	Left breast	94	54.7
	Unknown	1	0.6
ER mutation	Positive	136	79.1
	Negative	31	18
	Unknown	5	2.9
PR mutations	Positive	117	68
	Negative	49	28.5
	Unknown	6	3.5
HER2 mutation	Positive	55	32
	Negative	107	62.2
	Unknown	10	5.8
	Total	172	100
	N	Mean	Std. Deviation
Age (Years)	172	53.4	11
BMI	172	31.2	6

G1 (Well differentiated), G2 (Moderately differentiated), G3 (Poorly differentiated).

Table 2 Neoadjuvant chemotherapy response and last follow up status

		n	%
Type of Response	Complete remission (CR)	123	71.5
	Partial remission (PR)	20	11.6
	No change or stable disease (SD)	23	13.4
	Progressive disease (PD)	6	3.5
Status of Last F/U	Alive with CR	106	61.6
	Alive with PR	9	5.2
	Alive with SD	17	9.9
	Alive with PD	8	4.7
	Lost FU or deceased	32	18.6
	Total	172	100

*CR (complete disappearance of the tumor in the imaging or complete remission), PR (Partial remission>30%), SD (No change or stable disease or <25% increasing or decreasing tumor size), PD (>20% increasing in tumor size and metastasis with new lesion).

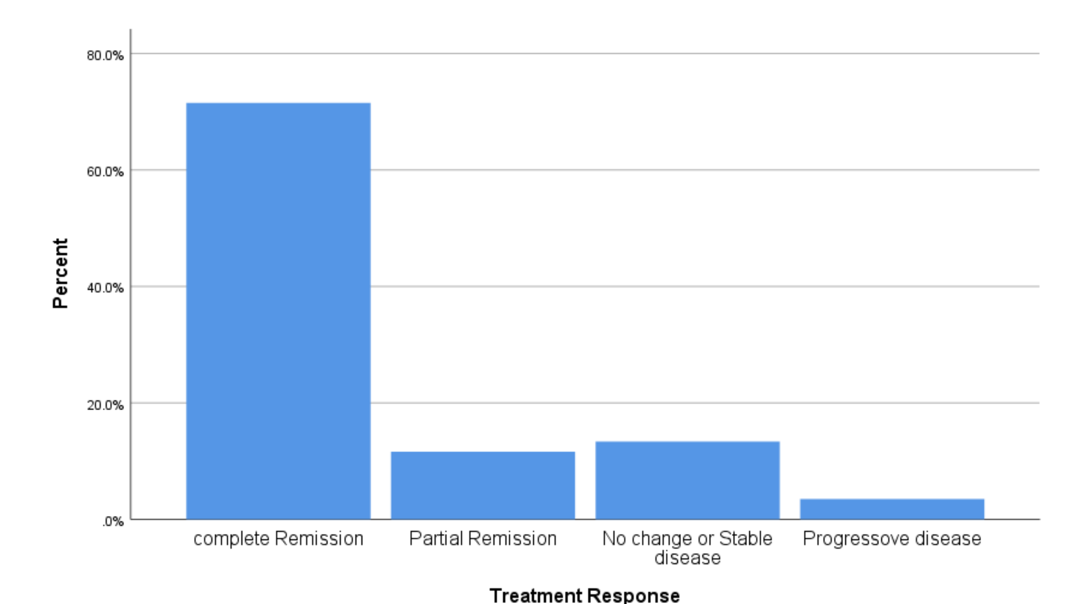


Figure 1 Treatment Response

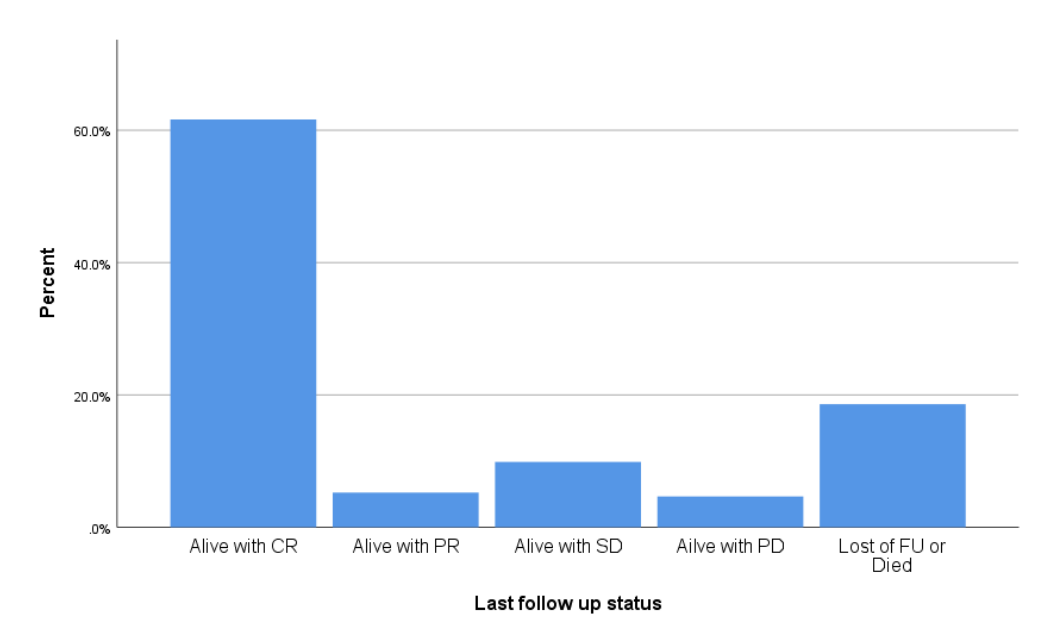


Figure 2 Last follow up Status

Association of inflammatory biomarkers and response type

The Red Cell Distribution Width (RDW) showed a P-value (0.003) and Neutrophil-Lymphocyte Ratio (NLR) with a P-value of (0.014), which reveals a significant positive result in chi-square related to the type of response after Neo-adjuvant chemotherapy in our study sample. Regarding RDW, A lot of patients in our study were within the normal level 146 (84.9%). On the other hand, NLR in many patients showed a low level of 145 (84.3%). All other parameters showed a non-significant P-value, the mean platelet volume (MPV) have been shown a normal level in most of the patients 153 (89%), lymphocyte to monocyte ratio (LMR) was also at a low level in 149 (86.6%), and platelet lymphocyte ratio (PLR) has a high level in 91 (52.9%) (Table 3).

Table 3 Association of inflammatory biomarkers and response type

Variables N=172	CR (N=123) N (%)	PR (N=20) N (%)	SD (N=23) N (%)	PD (N=6) N (%)	P value
NLR					
High >3	22(17.9%)	2(10%)	0(0%)	3(50%)	0.014
Low ≤3	101(82.1%)	18(90%)	23(100%)	3(50%)	
RDW					
High >14.1	22(17.9%)	2(10%)	0(0%)	0(0%)	0.003
Normal 11-14.1	100(81.3%)	18(90%)	23(100%)	5(83.3%)	
Low <11	1(0.8%)	0(0%)	0(0%)	1(16.7%)	
LMR					
High >6.2	15(12.2%)	4(20%)	2(8.7%)	2(30%)	0.673
Low ≤6.2	108(87.8%)	16(80%)	21(91.3%)	4(80%)	
PLR					
High >135	69(56.1%)	10(50%)	9(39.1%)	3(50%)	0.504
Low ≤135	54(43.9%)	10(50%)	14(60.9%)	3(50%)	

4. DISCUSSION

Breast cancer is the commonest lethal cancer among types of cancer in women's and the second most common cancer in the general population. The Predicted of prevalence for breast cancer globally among females of all ages in 2020 is 24.5%. It is a common malignancy among Saudi females, with an incidence of 29% in 2020 (GCO.iarfc, 2020). Neoadjvunt chemotherapy (NACT) is used in locally advanced and operable breast cancer patients and is now well established as a standard treatment option (Kaufmann et al., 2006; Untch et al., 2014; Maltoni et al., 2016). Despite surgical and chemotherapeutic treatments, approximately 30% of patients with negative axilla lymph nodes and 50% of patients with positive axilla lymph nodes may relapse within five years (Tao et al., 2015). Moreover, the tumor size, lymph node metastasis, the clinical stage, pathological grading, and molecular typing have traditionally been considered independent prognostic variables in breast cancer (Szkandera et al., 2013).

The outcomes of breast cancer and malignancies, in general, have other determinants besides tumor characteristics that have been mentioned. Recently the significance of host immune response reflected by inflammatory processes activated by malignant cells has been recognized and can determine the outcome of cancer patients (Hanahan et al., 2011). This inflammatory response resembles white cell counts (i.e., neutrophils, lymphocytes, platelets, and monocytes) and their combinations (e.g., NLR, PLR, and LMR) which are routinely performed for cancer patients in clinical practice pre and post-treatment, measuring of these parameters could have a beneficial impact in patients' evaluation during treatment and follow up strategies to identify deferent change patterns would contribute to optimizing best possible outcomes as other clinical investigators have been recognized the predictive role of

pre-treatment immune response in patients survival with deferent cancer variations (Guthrie et al., 2013; Coffelt et al., 2016; Ray-Coquard et al., 2009).

On the biological level of inflammatory response activated by tumor cells, there are deferent changes in circulating WBCs such as neutrophilia due to increased production of cytokines, which stimulates bone marrow and generates neutrophils. These alternations in immune response and information will promote and initiate tumor growth and progression, acting as a pro-metastatic factor (Franco et al., 2015; Goldrath et al., 1999). Similarly, Lymphocytopenia occurrence due to apoptosis by cancer cells was related to tumor burden, host characteristics, paraneoplastic inflammatory syndrome, metastatic sites and worse survival rate (Pierce et al., 2009; Ownby et al., 1983).

Further to that, chronic inflammation influences tumorigenesis by creating an environment enhanced by reactive oxygen and nitrogen radicals emitted by inflammatory cells involved in tumor pathology and thus propagating DNA changes in the host. Furthermore, specific body response to that reaction has a prognostic role among cancer patients by destroying normal cellular integrity leading to more deterioration and abnormal cellular proliferation (Hanahan et al., 2011; Strieter et al., 2006). This study aims to determine the clinical value of pre-treatment peripheral inflammatory biomarkers (PLR, NLR, LMR, RDW, and MPV) as a prognosis maker of response to neoadjvunt chemotherapy in locally advanced breast cancer (LABC). We found only two markers were significantly correlated with the type of response; low NLR (P value= 0.014) and Normal RDW (P value= 0.003) which reflect the neoadjvunt chemotherapy as a complete response.

Neutrophil-Lymphocyte Ratio (NLR) is an index reflecting immunological and inflammatory response levels, which has been studied in several types of tumors. The increase or decrease of NLR level indicates a Change in neutrophils or lymphocytes count, the high ratio reveals a decrease in lymphocyte level or araise in the neutrophil count relative to normal patients (Kaufmann et al., 2006). Primary source of circulating angiogenetic and growth factors are the Neutrophils, contributing to tumor growth and progression. In contrast, lymphocytes have a protective host response via cytotoxic cell death and cytokine production that inhibits tumor cell proliferation (de Larco et al., 2004; Agarwal et al., 2012).

Low Neutrophil-Lymphocyte Ratio (NLR) in our study shows a positive P value (0.014) associated with the complete response, which is the majority response in our study (71.5%) after neoadjvunt chemotherapy, reflecting a positive predictor to better outcome and prognosis among breast cancer patients. On the other hand, there is some studies suggest that high NLR count has an association with a low prognosis in breast cancer patients but is not fully understood because it may be indicative of inflammation. Neutrophils have a rule in a promote tumor growth by suppressing the activity of lymphocytes and T-cell response and inhibiting the immune system (de Gonzalo et al., 2012). The red width cell distribution width (RDW) is a measurement reflecting size variation of the circulating red blood cells. The main use of RDW was limited to microcytic hypochromic anemia to differentiate between iron deficiency anemia and thalassemia trait (Untch et al., 2014).

High RDW in different studies has been documented to be associated with various cardiovascular rheumatological and inflammatory disease outcomes. Furthermore, found to reflect an increase in circulating cytokines leading to the progressive status of inflammatory reaction. RDW could be a potential pre-treatment parameter among breast cancer patients and other oncological conditions. According to Seretis et al., (2013) they found that a high RDW has been reflecting a low outcome in breast cancer patients by reflecting cancer activity and progression. We suggest that controlling these parameters within standardized normal levels by adjusting the patient's health status before treatment and control other comorbidities that can affect these parameters and contribute to cancer progression and eventually poor outcome and overall survival. Applying individualized considerations for cancer patients according to the baseline of these markers, besides other tumor characteristics before treatment, can play a crucial role during the therapeutic plan and mentoring. Using NLR baseline level and follow trending patterns could be used for patient stratification and decision-making for the management plan and follow-up. Also, analyzing NLR patterns and variations, overtime may help to determine remission recurrence and prognosis, leading to early recognition and intervention and better outcomes.

Since that elevated NLR occurred due to alternated levels of neutrophils and lymphocytes mainly by neutrophilia, close mentoring for those patients should be considered besides the implication of neutrophils lowering agents for those with significant elevation of PMNs level. Neutrophils targeting drugs as reparixin CXCR1 and CXCR2 inhibitor, which inhibit the inflammatory reaction and neutrophil's function, could be used in combination with chemotherapeutic regimens to optimize best outcomes according to patients' stratification based on NLR baseline and patterns variations after critical assessment and evaluation to choose specific patients that will have a great benefit and most beneficial outcomes by initiating this combination.

5. CONCLUSIONS

According to the nature of our study, we have a few limitations. Our data were collected from a single center. Some overall survival information was lacking, the follow-up time was missed in some patients, and the relatively small sample size. Furthermore, the patient's characteristics may affect the level of inflammatory biomarkers in the peripheral blood. In summary, neoadjvunt chemotherapy with a low NLR and normal RDW among locally advanced breast cancer were significantly associated with the type of response after treatment.

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Ethical consideration

The ethical committee approved the study at King Abdulaziz University Hospital by the Biomedical Ethics Unit (#643-19).

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Conflict of interests

The authors declare that there are no conflicts of interests.

Data and materials availability

All data associated with this study are present in the paper.

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